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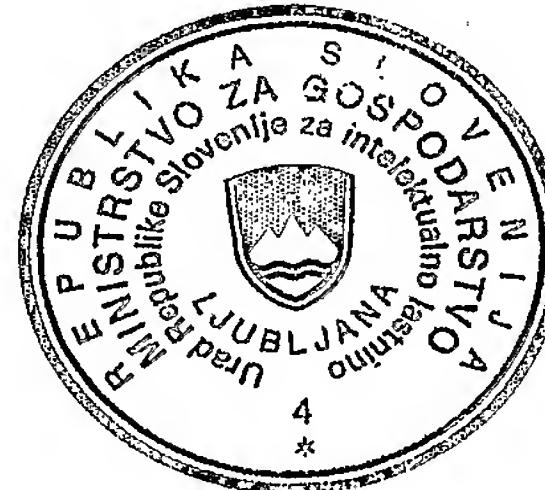
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(54) Naziv (*Title*):

Amoksicilin instant granulat

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Janez Kukec-Mezek  
podsekretar



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6. Podatki o zahtevani prednostni pravici in podlagi zanjo:

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9. Priloge:

opis izuma, ki ima 12 stran 2x  
 patentni zahtevek (zahtevki), ki ima(jo) 4 strani; število zahtevkov: 35 2x  
 skice (če so zaradi opisa izuma potrebne); število listov: 1 2x  
 povzetek 2x  
 potrdilo o plačilu prijavne pristojbine  
 potrdilo o deponiraju biološkega materiala, če gre za izum, ki ga ni mogoče drugače opisati  
 pooblastilo zastopniku  
 generalno pooblastilo zastopniku je deponirano pri uradu pod št.: \_\_\_\_\_  
 potrdilo o razstavni prednostni pravici  
 podatki o drugih prijaviteljih  
 podatki o drugih izumiteljih  
 prikaz zaporedja nukleotidov ali aminokislin v opisu  
 prijava je bila predhodno posredovana po faksu ali v elektronski obliki  
 \_\_\_\_\_

KOŠAK Alenka

Priimek in ime ter podpis prijavitelja (zastopnika)

## Amoxicillin instant granulate

### Field of the invention

(Int. Cl.: A 61 K 31/43, A 61 K 9/16)

The present invention relates to novel process for preparing a pharmaceutical granulate comprising amoxicillin trihydrate and a sugar, to a novel stable granulate comprising amoxicillin, preferably amoxicillin trihydrate and the sugar, for reconstitution with water into oral aqueous suspension formulation and to a method of treatment of bacterial infection in humans or animals.

### Technical problem

There is a constant need for preparing stable oral fine aqueous suspension comprising amoxicillin trihydrate, with palatable taste for use in pediatric patients and in the adults, especially in the geriatrics, obtained after reconstitution of granulate comprising amoxicillin trihydrate into aqueous suspension. Aqueous suspensions of said  $\beta$ -lactam antibiotic known in the art can be obtained by the reconstitution of granular product with water, wherein said antibiotic used for the preparation of granulate have to be preliminary prepared by way of grinding or micronising of said antibiotic and/or the addition of surface active substances to the composition in order to obtain applicable aqueous suspension formulations after reconstitution of granulate with water.

### Prior art

Amoxicillin is an antibacterial agent extensively used for the treatment of a wide range of bacterial infections. Amoxicillin in the form of the trihydrate is available on the market in a number of different formulations, for example, as granules or powders for oral suspension, hard gelatine tablets, capsules, chewable tablets, pediatric

drops. Different formulations and different amounts of amoxycillin are provided for adult and pediatric patients. Depending on the indications, the weight of the amoxicillin (as amoxicillin trihydrate) in unit dosage form for children and adults may range from 125 mg to 3 g. The largest film-coated tablet that can be manufactured contains a maximum of 1 g of the active substance. Children are unable, or to find it very difficult, to swallow tablets of that size. The problem with swallowing increases with the age of the patient and is found in the geriatric patients. For pediatric patients each 5 ml of reconstituted aqueous suspension comprising either 125 mg or 250 mg of amoxicillin as the trihydrate.

● Aqueous suspensions of amoxicillin trihydrate, obtained after reconstitution of water-soluble granulate in water, are mainly used in treating children and in elderly patients. Prior to administration to patients granulates comprising said  $\beta$ -lactam antibiotic for oral administration are suspended in an aqueous liquid. In this cases amoxicillin (as trihydrate) is usually mixed with suspension stabilisers (e.g. hydrocolloids or thickeners), buffers, preservatives, aromatic substances etc., together with a considerable amount of sugar, for example sucrose, and/or lactose, sugar alcohols, for example manitol or sorbitol, and maltodextrins to form granules being reconstitutable into aqueous suspension. The speed of absorption after administration of aqueous suspension of antibiotic to a patient is to a large extent dependent on the particle size of the crystals of said  $\beta$ -lactam antibiotic, on their wettability and on their suspensibility. A very fine aqueous suspension is required to achieve rapid absorption after administration to a patient.

Generally, this known object is obtained by way of preliminary step of grinding or micronizing of an antibiotic and/or the addition of surface active substances to the composition. More preferably, a micronized amoxicillin trihydrate is used in common granulating methods for preparing granulate, typically the majority of particles size of antibiotic in the granulate being less than 50  $\mu\text{m}$ .

Jato J.L. Vila and Pacheco R. Martinez, Ciencia & Industria Farmaceutica (1976), 8(11), 330-332, describes effect of particle size on the dissolution rate of amoxicillin trihydrate.

Normally, aqueous suspension formulations described in the prior art, lacks of suspension stability (the tendency to separate the active compound out again) and poor flowability of granular product, and for that object to obtain homogeneous and stable granules common granulating method such as wet granulation technique are used in the prior art processes. In order to obtain said object wet granulation process technique have to be carried out very carefully to avoid the agglomeration of the crystals of the antibiotic and, consequently, the formation of large, secondary particles of active substance with slow solubility and/or suspendability.

It is known from the prior art that granulate comprising active substance, e.g. amoxicillin trihydrate, which is filled into a suitable, single dose units, such as glass bottles, sachets, plastic tubes, for administration, or alternatively the granular formulations may be filled in jars as a multidose presentation for reconstitution into aqueous suspension. Shortly before the administration to the patients water is added to the granular formulation and the resulting dissolved product is shaken well to prepare an oral aqueous suspension. Various pharmaceutically acceptable excipients are necessary as the additive added during common granulation processes, for example lubricants, flavouring agents, sweetening agents, thickeners, suspending agents, disintegrants, dessicants, colours, dyes, preservatives, binders, to obtain granulate and further to achieve a good distribution of antibiotic into granulate to ensure stability of the resulting aqueous suspension during the period of administration to the patients and to prevent the growth of microorganisms during the time.

Aqueous suspensions of amoxicillin trihydrate prepared according to the processes known in the art contain antibiotic highly concentrated that not all of it dissolves in water. Dosage is normally carried out using a measuring spoon or, for smaller volumes, by means of a dosing syringe.

Granules containing penicillin, e.g. amoxicillin trihydrate being reconstitutable into aqueous suspension formulation and a process for their preparation by fluid bed

granulation is described in US patent No. 4,177,254. According to said process obtained granules contain particles or agglomerates of particles. Aqueous suspension obtained after reconstitution of granules in water suffers of lower speed of absorption and of other known drawbacks, described in the prior art.

The preparation of granules comprising amoxicillin trihydrate has been described in WO 92/19227 and WO 98/35672 wherein in a preferred process granules are prepared by roller compaction. WO 00/66169 describes a chewable tablet comprising amoxicillin in which the chewable base comprise essentially mannitol which is present in at least 25% by weight of the tablet useful for treating a wide range of bacterial infections in children. WO 03/063820 describes a process for the production of a granulate which is stable to segregation and which comprises granulate particles, which contain at least one  $\beta$ -lactam antibiotic, e.g. amoxicillin in the form of a trihydrate and at least one  $\beta$ -lactamase inhibitor, useful for the production of pharmaceutical compositions.

#### Description of the invention

The object of the present invention is to find a novel process for preparing stable granulate comprising amoxicillin trihydrate and to stable granulate comprising amoxicillin trihydrate as well, for reconstitution with water, to obtain fine stable homogeneous aqueous suspension, wherein the preliminary process step for preparing fine particle size of micronized antibiotic amoxicillin trihydrate used subsequently in the granulation processes as described in the art, for example grinding or micronizing, would be omitted.

Further is the object of the present invention to prepare stable granulate with good flow characteristics comprising amoxicillin trihydrate, wherein the addition of common pharmaceutically acceptable excipients known in the art, for example thickeners, lubricants, disintegrants, preservatives, dessicants, stabilizing agents, flavouring agents, dyes, suspending agents etc. would be also omitted and resulting granules would enable very rapid formation (e.g. from 10 to 60 seconds) of an aqueous

suspension in a small volume of water and the resulting aqueous suspension comprising amoxicillin trihydrate would be highly palatable and consequently easily swallowed by the patient, preferably by children and elder patients.

We have surprisingly and unexpectedly found that the problem known in the prior art has been solved by the novel process of the present invention, wherein amoxicillin trihydrate is compacted with a water soluble sugar or combinations of sugars, that is monosaccharides, disaccharides, oligosaccharides or polysaccharides, by means of commercially available extruder. Preferably, according to the novel process of the present invention amoxicillin trihydrate is compacted with the sugar (carbohydrate), preferably selected from the group consisting of sucrose, lactose, manitol, sorbitol, fructose, glucose, trehalose and maltodextrin alone or in combination, by means of said commercially available extruder, wherein the loss of crystallisation water of amoxicillin trihydrate caused by applied pressure and temperature between 30° to 100°C is compensated for by the addition of water. The resulting granulate is reconstituted prior to use with water into stable, homogeneous, fine and pleasant tasting aqueous suspension of amoxicillin trihydrate for human and animal patients, preferably in pediatric patients and in geriatrics.

More preferably, the granulate of the invention comprise sucrose as the sugar component.

Among the sugar alcohols manitol and sorbitol are preferably used for preparing granulate.

According to the process of the present invention an extrusion granulation is performed and water or aqueous solution of sugars, preferably sucrose, may be used as a granulation liquid to obtain an extruded wet granulation mass. A granulation mass appropriate for extrusion granulation may be obtained by mixing and sieving amoxicillin trihydrate and sugar, preferably sucrose, extruding obtained sieved mixture with water or aqueous solution of the sugar as extrusion granulation liquid. Preferably sucrose may be used as the sugar, but other sugar(s) alone or in

combinations of sugars, as described above, may be used as well. The amount of granulating liquid may be easily determined. The granulation mixture is extruded, e.g. at appropriate extrusion temperatures, e.g. between 30° to 100°C, to obtain wet extruded mass of amoxicillin trihydrate. The obtained wet extruded mass is screened through a sieve, preferably oscillating sieve, subsequently dried the obtained sieved extruded wet mass which is screened again through a sieve, preferably oscillating sieve. Dried and sieved extruded mass is homogenized to obtain granulate comprising amoxicillin trihydrate. A preferred mesh size of the sieve used in the process is in the range between 0.5 mm to 4.0 mm, preferably in the range of 1 mm to 2 mm.

Amoxicillin trihydrate in the form of granulate for reconstitution with water into aqueous suspension may be prepared according to a process of the present invention comprising the steps:

- a. sieving the mixture of amoxicillin trihydrate and the sugar
- b. extruding sieved mixture with water or aqueous solution of sugar as a granulation liquid to obtain a wet extruded mass,
- c. screening the extruded wet mass through a sieve
- d. drying the sieved extruded wet mass
- e. dried and sieved extruded mass is homogenized to the granulate
- f. obtained granulate are easily dissolved in water to form smooth suspension immediately.

We have unexpectedly found that according to the process of the invention the fine micronized particles of amoxicillin trihydrate are obtained in the course of novel process itself and the preliminary process step known in the art, for example grinding or micronizing of said antibiotic necessary for subsequent granulation process, is omitted.

We have also unexpectedly found that other pharmaceutically acceptable excipients such as commonly used in pharmaceutical formulation technology for granulation

process as described above, may be omitted as well. Preferably, no pharmaceutically acceptable excipient is added during the whole extrusion granulation process in order to obtain granulated amoxicillin trihydrate and the sugar, free of any excipient. Granulate obtained in the process of the present invention is stable even without addition of any stabilizing agent or other excipients. With good reason we may designate the novel granulate of the present invention "amoxicillin instant granulate".

The micronized particles of amoxicillin in the granulate obtained according to the process of the present invention are in the size range between 0.1  $\mu\text{m}$  to 100  $\mu\text{m}$ , preferably between 0.5  $\mu\text{m}$  to 50  $\mu\text{m}$ .

Preferred amoxicillin granulate comprise from 1 to 80 weight %, preferably between 5 to 50 wt. %, more preferably between 10 to 30 wt. % of amoxicillin trihydrate and from 20 to 99 weight %, preferably from 70 to 90 wt. % of sucrose.

In one aspect, amoxicillin granulate comprise from 20 to 90%, preferably between 70 to 90 % of the water soluble sugar, selected from the group consisting of sucrose, lactose, manitol, sorbitol, fructose, glucose and maltodextrin alone or in combination. Mixtures of said sugars and sucrose may also be used.

A preferred mean particle size of the granules is in the range between 200  $\mu\text{m}$  to 3000  $\mu\text{m}$ , particularly between 500  $\mu\text{m}$  to 1500  $\mu\text{m}$ .

Aqueous suspensions comprising amoxicillin trihydrate and the sugar obtained after reconstitution of granulate of the present invention with water are suitable even for the administration of larger amounts of the antibiotic, for example 5 g in 50 ml suspension.

In a further aspect, the present invention provides a process for the production of granulate, comprising optionally adding further pharmaceutically acceptable excipient(s) to a granulate afterwards e.g. for admixing said excipients with the granulate obtained by a process according to the present invention if for the final

application of aqueous suspension formulation of said  $\beta$ -lactam antibiotic such a formulation would be suitable for human or animal patients.

The process of the present invention provide a solid suspension of fine micronized particles of amoxicillin trihydrate in sugars, preferably in the sugar, selected from the group consisting of sucrose, lactose, manitol, sorbitol, fructose, glucose and maltodextrin alone or in combinations, more preferably in sucrose. The micronized particle size of said  $\beta$ -lactam antibiotic after dissolution of resulting granulate with water into aqueous suspension corresponds to that of dry amoxicillin trihydrate obtained by preliminary process step of micronizing the antibiotic.

In a further aspect, antibiotic may be pre-wetted with the sugar to obtain a granulate and when said granulate is dissolved in water, ensures rapid formation of a homogeneous aqueous suspension of amoxicillin trihydrate.

The fineness, homogeneity and good perfusion provide an aqueous suspension of amoxicillin obtained after reconstitution of granulate with water, and obtained suspension is considerably less prone to sedimentation of the particles of antibiotic, even without addition of thickeners and other pharmaceutically acceptable excipients.

Rapidly obtained, fine aqueous suspension of the present invention ensures good and stable bioavailability of amoxicillin trihydrate, irrespective of the storage time of the obtained aqueous suspension.

Figure 1 and Figure 2 show the comparision between the distribution of micronized particle size of amoxicillin trihydrate in aqueous suspension obtained immediately after reconstitution of granulate with water and after storage of obtained aqueous suspension for 24 hours. From the comparision of both Figures it is easily seen that only granules obtained according to the novel process of the present invention (sample D) lead to an aqueous suspension without formation of any major agglomerates. All particles of said  $\beta$ -lactam antibiotic in the suspension are in the size of less than 50  $\mu\text{m}$ , the major particles being within the range from 1  $\mu\text{m}$  to 30

μm, even shortly after reconstitution of granules with water into aqueous suspension and which shows no alteration during storage.

In Figures 1 and 2 sample A means the distribution of particles size of amoxicillin trihydrate obtained after reconstitution of granulate into aqueous suspension, wherein said granulate is obtained according to wet granulation technique, known in the art. Sample B means the distribution of particle size of antibiotic obtained after reconstitution of dry mixture of mainly saccharose, xanthan gum and surfactant (glycerolmonooleate) with micronized amoxicillin trihydrate which is obtained preliminary by the methods known in the art. Sample C means the distribution of particle size of antibiotic obtained after reconstitution of the mixture of preliminary untreated amoxicillin trihydrate and sucrose into aqueous suspension and sample D means the distribution of particle size of amoxicillin trihydrate obtained after reconstitution of the novel granulate of the present invention into aqueous suspension.

The granulate obtained according to the present invention is filled into glass bottles, packed in unit dose sachets or other suitable container. A granular product may be used at a range of unit doses, for example 125 mg, 250 mg, 500 mg, 1 g and 3 g of amoxicillin trihydrate. The dosage forms makes it very easy to prepare also large amounts of antibiotic in relatively small quantities of water for patient friendly administration.

In a further aspect, homogeneous diluted aqueous suspensions or solutions of amoxycillin trihydrate may be obtained rapidly by simple stirring of granulates of the present invention with drinking water for the treatment of bacterial infections in animals and domestic animals such as cattle, calves, horses, pigs, sheep, lambs, dogs, cats, poultry /chickens, ducks, geese, turkeys.

Obtained diluted aqueous suspensions or solutions of amoxicillin trihydrate according to the present invention are stable for several days, up to 14 days at room temperature.

The invention also provides granulates comprising amoxicillin trihydrate and the sugar and aqueous suspensions obtained by reconstitution of said granulate with water for use in the treatment of bacterial infections.

The invention also provides a method of treatment of bacterial infections in humans and animals which comprises the administration of a therapeutically effective amount of aqueous suspensions obtained by reconstitution of granulates, comprising amoxicillin trihydrate and the sugar, with water.

The invention is illustrated by the following Examples:

Example 1: Granulate

Component	Weight (g)
Amoxicillin trihydrate	200
Sucrose	800

Amoxicillin trihydrate and sucrose are sieved together through 1.0 mm sieve, mixed in a tumbler mixer and afterwards extruded through the extruder (Theysohn TSK N20/20D - Maschinenbau / Salzgitter (Germany)) by water flow rate of 1 g/min and a resulting mass flow of 30 g/min.

The obtained wet mass is screened by using an oscillating sieve through a 2.0 mm sieve and dried in a fluid bed dryer with an inlet air temperature of 60°C about 5 min. After drying, the extruded product obtained is screened once again through a 1 mm oscillating sieve and then homogenized in a tumbler mixer to obtain granulate of amoxicillin trihydrate.

Example 2: Granulate

Component	Weight (g)
Amoxicillin trihydrate	100
Sucrose	900

Solution for extrusion granulation:

Component	Weight (g)
Water	100
Sucrose	200

200 g sucrose is dissolved in 100 g warm water and allowed to cool to room temperature to obtain solution for extrusion (stock solution, only a part is needed for extrusion – approximately 35 g).

Amoxicillin trihydrate and sucrose are sieved together through 1.0 mm sieve, mixed in a tumbler mixer and afterwards extruded through the extruder (Theysohn TSK N20/20D) by preliminary prepared aqueous sucrose solution and flow rate of 3 g/min and a resulting mass flow of 30 g/min.

The obtained wet mass is screened by using an oscillating sieve through 2.0 mm sieve and dried in a fluid bed dryer with an inlet temperature of 60°C about 5 min. After drying, extruded product is screened once again through 1.0 mm oscillating sieve and then homogenized in a tumbler mixer to obtain granulate.

Example 3: Granulate

Component	Weight (kg)
Amoxicillin trihydrate	20
Sucrose	80

**Solution for extrusion granulation:**

Component	Weight (kg)
Water	10
Sucrose	20

20 kg sucrose is dissolved in 10 kg warm water and allowed to cool to room temperature to obtain solution for extrusion (stock solution, only a part is needed for extrusion – approximately 12 kg).

Amoxicillin trihydrate and sucrose are sieved together through 1.0 mm sieve, mixed in a tumbler mixer and afterwards extruded through the extruder (Werner Pfeiderer extruder) by preliminary prepared aqueous sucrose solution and flow rate of 12 kg/h and resulting mass flow of 100 kg/h.

The obtained wet mass is screened by using an oscillating sieve through 2 mm sieve and dried in a fluid bed dryer. After drying, the extruded product obtained is screened once again through 1.0 mm oscillating sieve and then homogenized in a tumbler mixer to obtain granulate.

## Claims

1. A process for preparing a stable granulate for reconstitution with water into an oral aqueous suspension comprising amoxicillin trihydrate and a sugar, the process comprising the following steps:
  - a. sieving the mixture of amoxicillin trihydrate and the sugar
  - b. extruding sieved mixture with water or aqueous solution of the sugar as granulation liquid to obtain a wet extruded mass
  - c. screening the extruded wet mass through a sieve
  - d. drying the sieved extruded wet mass
  - e. dried and sieved extruded mass is homogenized to the granulate
  - f. obtained granulate is dissolved in water to form smooth suspension immediately.
2. A process according to claim 1, wherein the sugar is selected from the group consisting of sucrose, lactose, sugar alcohols and maltodextrins alone or in combination.
3. A process according to claim 1, wherein the sugar is sucrose.
4. A process according to claim 2, wherein the sugar alcohol is manitol or sorbitol.
5. A process according to claim 1, wherein amoxicillin trihydrate is present in from 1 to 80% by weight of the granulate.
6. A process according to claim 1, wherein amoxicillin trihydrate is present in from 5 to 50% by weight of the granulate.
7. A process according to claim 1, wherein amoxicillin trihydrate is present in from 10 to 30% by weight of the granulate.

8. A process according to claim 1, wherein sucrose is present in from 20 to 99% by weight of the granulate.
9. A process according to any one of claims 1 to 8, wherein the particle size of the granulate is in the range of 200 to 3000  $\mu\text{m}$ .
10. A process according to claim 9, wherein the particle size of the granulate is in the range of 500 to 1500  $\mu\text{m}$ .
11. A process according to any of claims 1 to 10, wherein no pharmaceutically acceptable excipient is added during the process.
12. A process as claimed in any of claims 1 to 10, wherein optionally pharmaceutically acceptable excipient is added during the process.
13. A process for preparing free flowing granulate for filling into glass bottles, unit dose sachets or into other suitable container, used for reconstitution into an aqueous suspension, which process comprises preparing granulates according to any one of the preceding claims.
14. A granulate comprising amoxicillin trihydrate and a sugar.
15. A granulate according to claim 14 for reconstitution into an aqueous suspension.
16. A granulate according to claims 14 to 15, wherein the sugar is selected from the group consisting of sucrose, lactose, sugar alcohols and maltodextrins alone or in combination.
17. A granulate according to claims 14 to 15, wherein the sugar is sucrose.

18. A granulate according to claims 14 to 16, wherein the sugar alcohol is manitol or sorbitol.
19. A granulate according to claims 14 to 18, wherein amoxycillin trihydrate is present in from 1 to 80% by weight of the granulate.
20. A granulate according to claims 14 to 18, wherein amoxicillin trihydrate is present in from 5 to 50% by weight of the granulate.
21. A granulate according to claims 14 to 18, wherein amoxicillin trihydrate is present in from 10 to 30% by weight of the granulate.
22. A granulate according to claims 14 to 17, wherein sucrose is present in from 20 to 99% by weight of the granulate.
23. A granulate according to claims 14 to 17, wherein sucrose is present in from 70 to 90% by weight of the granulate.
24. A granulate according to any one of claims 14 to 23, wherein the particle size of a granulate is in the range of 200 to 3000  $\mu\text{m}$ .
25. A granulate according to any one of claims 14 to 24, wherein the particle size of the granulate is in the range of 500 to 1500  $\mu\text{m}$ .
26. A granulate according to claims 14 to 25, wherein the granulate contain no pharmaceutically acceptable excipient.
27. A granulate according to claims 14 to 25, wherein the granulate optionally contain pharmaceutically acceptable excipient.
28. A granulate according to claims 14 to 27, which is free flowing and which is provided in glass bottles, unit dose sachets or in other suitable container.

29. A granulate comprising amoxicillin trihydrate and the sugar according to any one of claims 14 to 28, wherein the granulate is reconstituted with water into an aqueous suspension which can be swallowed by a patient.
30. An aqueous suspension for oral administration to humans or animals comprising amoxicillin trihydrate and the sugar obtained after reconstitution of the granulate, prepared according to any one of the preceding claims, with water into an aqueous suspension.
31. A granulate comprising amoxicillin trihydrate and the sugar, free of any pharmaceutically acceptable excipient.
32. A granulate according to any one of the preceding claims provided for pediatric use which is reconstituted with water into an aqueous suspension prior to use.
33. A sachet product containing free flowing granulate, which comprises amoxicillin trihydrate and the sugar in a suitable unit dose, for reconstitution with water into an aqueous suspension immediately prior to use.
34. A method of treatment of bacterial infections in humans or animals, which comprises the administration of a therapeutically effective amount of the granulate comprising amoxicillin trihydrate and the sugar.
35. The use of granulate comprising amoxicillin trihydrate and the sugar in the manufacture of a medicament for treating bacterial infections.

### Abstract

A novel process for preparing stable granulate which comprises amoxicillin trihydrate and a sugar, and to novel stable granulate comprising amoxicillin trihydrate and the sugar as well, for reconstitution with water into fine stable homogeneous aqueous suspension is described. The novel process omits preliminary process step for preparing fine particle size of micronized amoxicillin trihydrate used subsequently in the granulation process known in the art, for example grinding or micronizing of said antibiotic.

In a preferred aspect the novel stable granulate comprises amoxicillin trihydrate and the sugar, preferably sucrose, free of any pharmaceutically acceptable excipient.

Novel granulate, which is easily dissolved in water to form smooth aqueous suspension immediately, is used for treating bacterial infections in humans or animals, especially in pediatric patients and in the geriatrics.

Figure 1

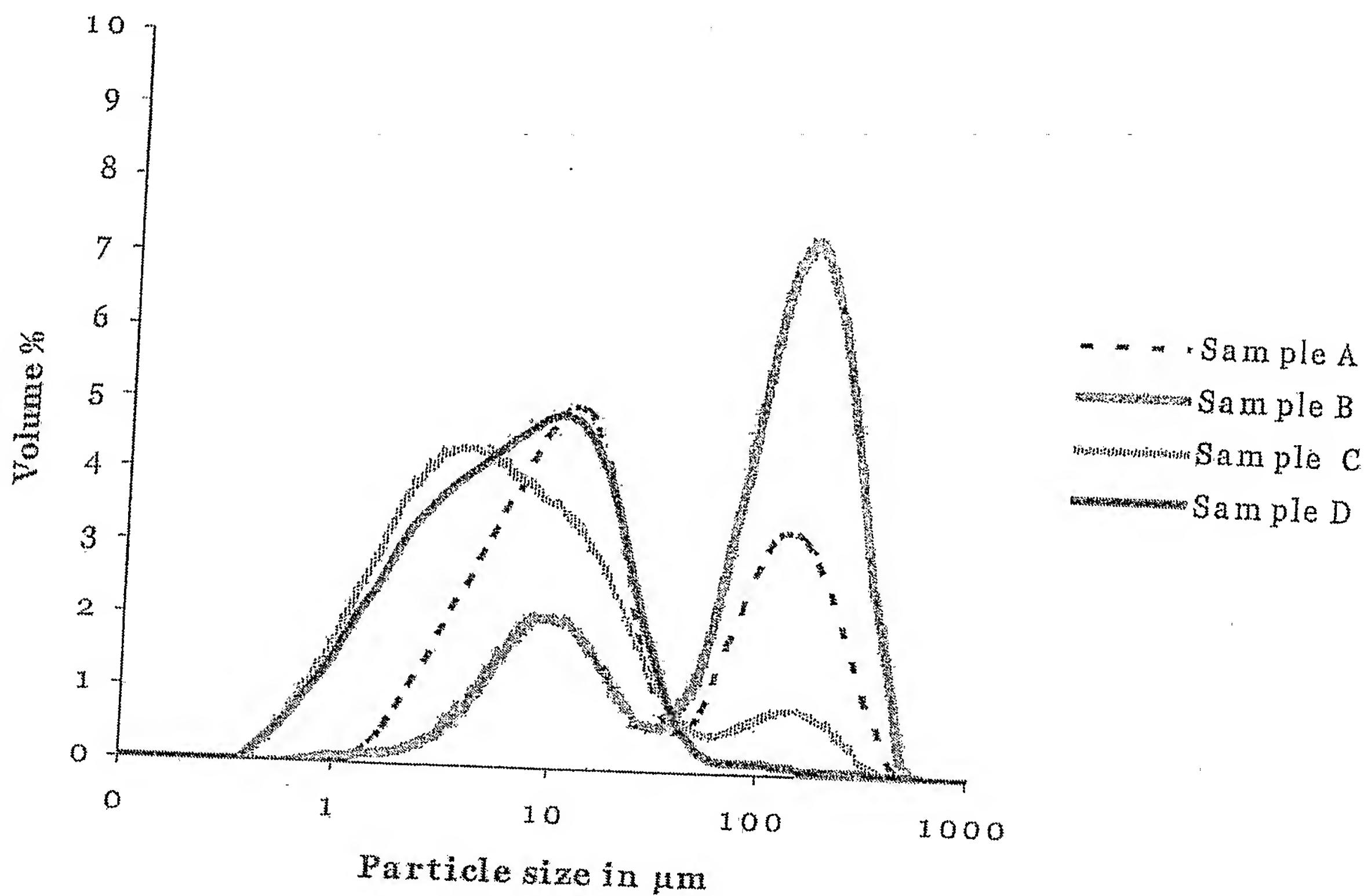


Figure 2

